**Neoadjuvant chemotherapy and radical surgery versus exclusive radiotherapy in locally advanced squamous cell cervical cancer: results from the Italian multicenter randomized study.**

# Neoadjuvant Chemotherapy and Radical Surgery Versus Exclusive Radiotherapy in Locally Advanced Squamous Cell Cervical Cancer: Results From the Italian Multicenter Randomized Study

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***Purpose:*** **Neoadjuvant chemotherapy (NACT) and radical surgery (RS) have emerged as a possible alternative to conventional radiation therapy (RT) in locally advanced cervical carcinoma. In 1990, a phase III trial was undertaken to verify such a hypothesis in terms of survival and treatment-related morbidity.**

***Patients and Methods:*** **Patients with squamous cell, International Federation of Gynecology and Obstetrics stage IB2 to III cervical cancer were eligible for the study. They received cisplatin-based NACT followed by RS (type III to V radical hysterectomy plus systematic pelvic lymphadenectomy) (arm A) or external-beam RT (45 to 50 Gy) followed by brachyradiotherapy (20 to 30 Gy) (arm B).**

***Results:*** **Of 441 patients randomly assigned to NACT+RS or RT, eligibility was confirmed in 210 and 199 patients, respectively. Treatment was administered according to protocol in 76% of arm A patients and 72% of arm B patients. Adjuvant treatment was delivered in 48 operated patients (29%). There was no evidence for any significant excess of severe morbidity in one of the two arms. The 5-year overall survival (OS) and progression-free survival (PFS) rates were 58.9% and 55.4% for arm A and 44.5% and 41.3% for arm B ($P = .007$ and $P = .02$), respectively. Subgroup survival analysis shows OS and PFS rates of 64.7% and 59.7% (stage IB2-IIB, NACT+RS), 46.4% and 46.7% (stage IB2-IIB, RT) ($P = .005$ and $P = .02$), 41.6% and 41.9% (stage III, NCAT+RS), 36.7% and 36.4% (stage III, RT) ($P = .36$ and $P = .29$), respectively. Treatment had a significant impact on OS and PFS.**

***Conclusion:*** **Although significant only for the stage IB2 to IIB group, a survival benefit seems to be associated with the NACT+RS compared with conventional RT.**

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SURVIVAL OF WOMEN with locally advanced cervical cancer has remained substantially unchanged during the last two decades. The long-term outlook is grim, with overall 5-year survival rates of approximately 40% when conventional treatments are used.[1-4] Neoadjuvant chemotherapy (NACT) followed by radical surgery (RS) has emerged as a valid alternative for investigation. The main objectives of preoperative chemotherapy are the potential elimination of micrometastases and shrinkage of the primary tumor bulk to achieve radical operability. Encouraging results were reported from different pilot studies that used this approach.[5-17] In particular, a 48% to 100% operability rate was observed after NACT with no influence on surgery-related morbidity, pathologically confirmed complete responses were detected in 9% to 18%, and the incidence of lymph node metastases was much lower than expected for the same stage and tumor size.[5-17] More important, the observed 5-year survival rates (83% and 45% for the stage IB2 to IIB and III groups, respectively) strongly suggested a cure benefit from NACT when it was followed by RS compared with exclusive radiation therapy (RT).[4,12-14] On the other hand, in the early 1990s, preliminary data from randomized trials on NACT preceding RT did not show any survival advantage with respect to RT alone.[18,19] Therefore, based on the above considerations, an Italian multicenter randomized trial was undertaken in 1990 to compare the efficacy and toxicity of sequential NACT and RS versus exclusive RT, taken as standard treatment, in patients with locally advanced cervical carcinoma.

## PATIENTS AND METHODS

Patients aged less than 70 years with untreated, locally advanced (International Federation of Gynecology and Obstetrics [FIGO] stage IB2 to III) squamous cell carcinoma of the uterine cervix were eligible. Criteria for exclusion were Eastern Cooperative Oncology Group performance status greater than 2, severe systemic disease, other malignancy (except for adequately treated basal cell carcinoma), pre-existing peripheral neuropathy and/or hearing loss, inadequate bone marrow reserve (WBC $< 4{,}000/mm^3$ and/or platelet count $< 100{,}000/mm^3$), and abnormal hepatic (serum bilirubin $> 1.5$ mg/dL) and renal

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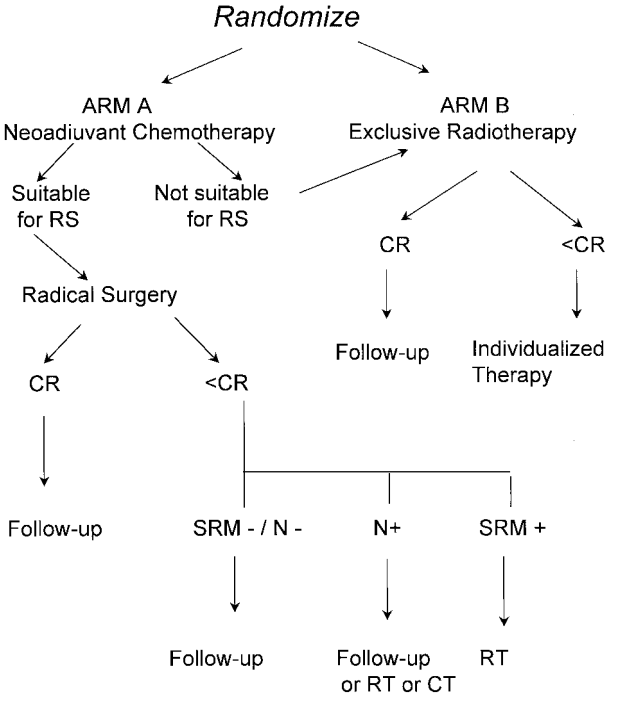


**Fig 1. Study design. Abbreviations: RS, radical surgery; CR, complete response; SRM −/+, surgical resection margins negative/positive; N −/+, lymph node–negative/positive; RT, radiotherapy; CT, chemotherapy.**

(creatinine clearance < 60 mL/min and/or serum creatinine > 1.2 mg/100 mL) functions. The clinical staging procedure was performed according to the system adopted by FIGO.[20] Abdominal and pelvic computed tomography or magnetic resonance imaging was also included in the staging work-up; abdominal lymphangiography was optionally performed. Informed consent was to be obtained from the patients. The study was examined and approved by the ethical committees in each participating center.

### *Treatment Plan*

Patients were randomized to either NACT followed by RS or exclusive RT. The study design is detailed in Fig 1. The NACT regimen was not predetermined, but minimal requirements were a cisplatin-containing regimen with a ≥ 240 mg/m$^2$ total cisplatin dose with a maximum of two additional drugs, administered over a period of 6 to 8 weeks. After NACT, the patients were clinically reassessed and classified as suitable or unsuitable for RS. The latter patients were treated by RT. RS consisted of radical hysterectomy (type III to V)[21] plus systematic (at least 20 nodes to be resected) pelvic lymphadenectomy (aortic lymphadenectomy was optional). Postoperative RT was given in patients with positive surgical resection margins and/or metastatic nodes. In the case of node metastasis, the choice of adjuvant treatment was based on the institution's policy (ie, chemotherapy, external-beam RT, or no further therapy).

Conventional treatment consisted of external-beam, megavoltage RT (45 to 50 Gy) to the whole pelvis over 5 to 6 weeks. In the presence of metastatic pelvic nodes, detected by computed tomography/magnetic resonance imaging or lymphangiography, an extra dose of 5 to 7 Gy was administered. Intracavitary low-dose-rate brachytherapy (20 to 30 Gy to the tumor volume) was provided 2 to 4 weeks after external RT. According to International Commission on Radiation Unit report 38,[22] the dose was prescribed to tumor volume, without a fixed minimum dose at point A. Aortic node metastases, when present, were irradiated (45 Gy/5 weeks, followed by a 5-Gy boost to residual disease eventually detected) with extended fields encompassing pelvic and aortic volume or at the end pelvic irradiation, in the case of a pelvic complete remission. Salvage treatments were allowed in patients who showed progressing disease.

NACT-induced toxicity was evaluated according to World Health Organization criteria,[23] and surgery and RT-related morbidities were classified using the French-Italian glossary of complications.[24] Patients were followed up 1 month after completion of treatment, every 3 months for the first 2 years, and at 6-month intervals thereafter. Local and distant failures were defined as disease recurring inside and outside the true pelvis (including aortic nodes), respectively. All case report forms were reviewed first by two study members and further verified by two independent investigators (one radiotherapist and one surgeon).

### *Randomization and Statistical Considerations*

Patients were randomly assigned to NACT&RS or RT by telephoning the trial data center. They were stratified at randomization by disease stage (IB2 to IIA > 4cm; IIB; III), age (≤ 60 years; > 60 years), and institution.

The main end point of the study was (overall and progression-free) survival. Sample size (400 patients) and a minimum follow-up of 2 years were planned to detect a 20% difference in outcome between the two arms (with a power of 80% at a significance level of 5%). Patient characteristics were compared by $\chi^2$ test. Survival curves were computed using the method of Kaplan and Meier,[25] and the differences were compared by the log-rank test. The main statistical analysis was done by intention to treat. Survival comparisons were also done for all eligible patients and for those receiving treatment according to the protocol. Cox's proportional-hazards regression model was used to adjust for possible prognostic factors.[26]

## RESULTS

### *Patients*

Between January 1990 and July 1996, 441 patients were randomized from 14 Italian centers. Most of the patients (371, 84%) were from the six main participating institutions. Thirty-two (7%) of the randomly assigned patients were ineligible to participate further (17 NACT&RS patients, 15 RT patients) (Fig 2). Therefore, a total of 409 eligible patients received treatment as assigned (210 NACT&RS patients, 199 RT patients). The baseline characteristics of eligible patients show no statistically significant differences between the two arms (Table 1).

### *Delivery of Planned Treatment*

The analysis of treatment revealed that 58 (25.5%) and 55 patients (28%) in the NACT&RS and RT arms, respectively, had protocol deviations (Fig 2). In particular, 2% of randomized patients received no treatment and 6% underwent alternative treatment, while assigned treatment was

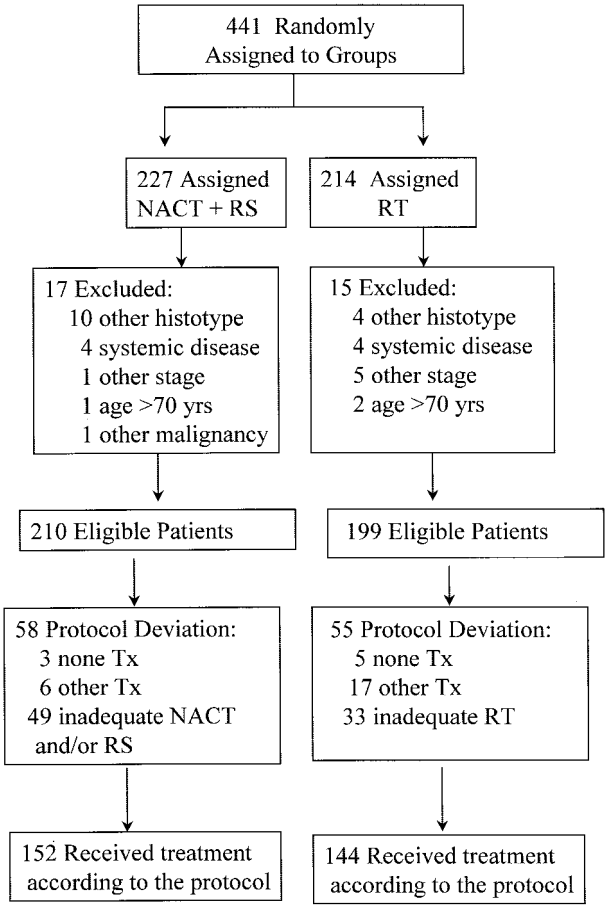


**Fig 2. Trial profile.**

**Table 1. Characteristics of the Patients**

| Characteristic | Arm A (n = 210) No. | Arm A (n = 210) % | Arm B (n = 199) No. | Arm B (n = 199) % |
|---|---|---|---|---|
| Age, years | | | | |
| Median | 49 | | 52 | |
| Range | 25-70 | | 28-69 | |
| Performance status | | | | |
| 0 | 197 | 94 | 181 | 91 |
| 1-2 | 13 | 6 | 18 | 9 |
| FIGO stage | | | | |
| IB2 to IIA > 4 cm | 87 | 41 | 87 | 44 |
| IIB | 72 | 35 | 76 | 38 |
| III | 51 | 24 | 36 | 18 |
| Tumor size > 5 cm | 113 | 54 | 115 | 58 |
| WHO grade | | | | |
| 1-2 | 133 | 63 | 123 | 62 |
| 3 | 71 | 34 | 65 | 32 |
| Ungraded | 6 | 3 | 11 | 6 |
| Lymph node status | | | | |
| Negative | 145 | 69 | 148 | 74 |
| Positive | 49 | 23 | 43 | 22 |
| Positive aortic | 11 | 5 | 7 | 3 |
| Unknown | 16 | 8 | 8 | 4 |

Abbreviation: WHO, World Health Organization.

inadequate for 49 (23%) and 33 patients (16.5%) in the NACT&RS and RT arms, respectively. In the NACT&RS arm, the reasons for inadequate treatment were as follows: more than 20% cisplatin total dose reduction (one patient) or more than 2-week delay of NACT administration (11 patients), in the absence of toxicity; selective (< 20 nodes resected) pelvic lymphadenectomy; and type II radical hysterectomy (40 patients) (more than one reason present in three patients). In the RT arm, the reasons were that a less than 60-Gy total dose (point A) was delivered in 21 patients and that in 18 patients the total treatment time was ≥ 90 days (more than one violation present in six patients).

*Chemotherapy*

The following chemotherapy regimens were used: (1) cisplatin and bleomycin (cisplatin 80 mg/m$^2$ on days 1 and 2; bleomycin 15 mg/m$^2$ on days 1 and 8) every 3 weeks for two courses (96 patients, 48%); (2) cisplatin, vincristine, and bleomycin (cisplatin 50 mg/m$^2$, vincristine 1 mg/m$^2$, and bleomycin 30 mg over 24 hours) for six weekly courses (66 patients, 33%); (3) cisplatin and ifosfamide (cisplatin 43 mg/m$^2$ and ifosfamide 3.5 mg/m$^2$ only on cycles 1, 4, and 7) for seven weekly courses (20 patients, 10%); and (4) single-agent cisplatin (at 40 mg/m$^2$) for six weekly courses (19 patients, 9%). The median cisplatin total dose administered was 300 mg/m$^2$ (range, 150 to 320 mg/m$^2$), and the median duration of NACT was 39 days (range, 16 to 56 days).

Due to toxicity, NACT was discontinued in 11 cases (5%), delayed (from 1 to 2 weeks) in 30 cases (15%), and dose-reduced in seven cases (3%). Treatment-affecting toxicity mainly consisted of moderate to severe myelotoxicity (grade 2 to 4 leukopenia or thrombocytopenia and/or grade 3 anemia; 87%) and mild to severe (transient) nephrotoxicity (6%). Cardiotoxicity (transient grade 3 arrhythmia) and hepatotoxicity (grade 3 AST elevation) were the causes of chemotherapy discontinuation in two patients; these two patients subsequently underwent RT.

*Surgery*

One hundred sixty-four patients (78%) were operated on, 37 (18%) were judged not amenable for RS, and nine patients (4%) received a completely different or no treatment and were excluded from this analysis. In particular, 26 patients (13%) showed stable (7%) or progressive disease (6%) at clinical reassessment, and two patients (1%) were shifted to exclusive RT due to chemotherapy-related toxicity; also, in nine patients (4%), RS was abandoned at

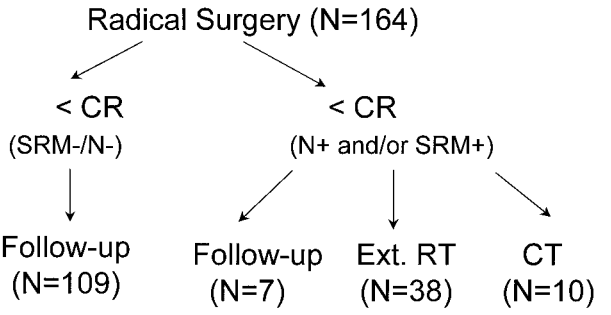


**Fig 3. Postoperative management. Abbreviations: CR, complete response; SRM −/+, surgical resection margins negative/positive; N −/+, lymph node–negative/positive; Ext. RT, external radiotherapy; CT. chemotherapy.**

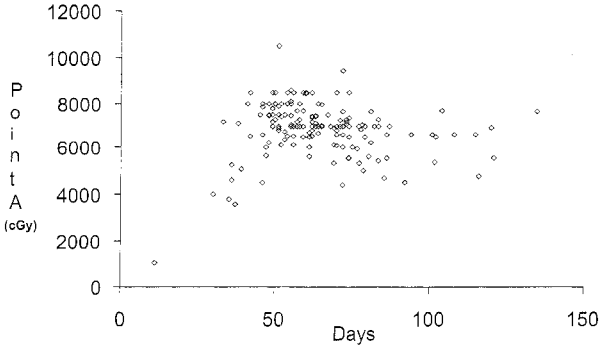


**Fig 4. RT: correlation between dose and time. All patients allocated to the RT are included.**

laparotomy (due to intraperitoneal or perilymph node disease spread, pelvic fibrosis, or unresectable primary tumor). Type III to IV radical hysterectomy was performed in 150 patients (91%) and type V in four patients (2%), while 10 patients (5%) underwent type II radical hysterectomy based on the decision of the treating physician. Systematic pelvic lymphadenectomy was performed in 130 patients (79%), with a median number of nodes resected of 36 (range, 20 to 81). Thirty-four patients (21%) underwent selective pelvic lymphadenectomy (median, 14 nodes; range, six to 19 nodes), and 77 patients (47%) underwent aortic lymphadenectomy (median, 18 nodes; range, one to 42 nodes), on the basis of the decision of the treating surgeon.

Pathologic examination of the surgical specimens revealed no residual cervical tumor in 22 cases (13%) and microinvasive disease only in a further 13 (8%). There was no evidence of significant differences among the various regimens used with respect to induction of pathologic response (data not shown). Parametrial and vaginal specimens were positive in 38 (23%) and 32 cases (19.5%), respectively. Pelvic and aortic lymph nodes were involved in 48 (29%) and four patients (2%), respectively, with no cases of isolated aortic metastasis. In particular, 10 metastatic nodes (34%) were found in the 29 operated patients with positive nodes at the staging work-up. On the other hand, 35 patients (29%) with clinically negative lymph nodes had positive results at pathologic examination.

Extracervical disease (parametria, n = 2; vagina, n = 3; nodes, n = 4) was detected in seven (20%) of the 35 patients who showed no frankly invasive tumor in the cervical specimen.

Surgical resection margins were positive in 11 patients (7%), four of whom also showed metastatic nodes. Therefore, a total of 55 patients were eligible for adjuvant treatment (Fig 3). Based on the protocol rules, this consisted of external RT (n = 38) or chemotherapy (n = 10); moreover, seven (16%) of the 44 patients with node metastasis (and negative surgical resection margins) received no further treatment.

*RT*

After external-beam RT to the whole pelvis, intracavitary RT was used in all but 50 patients (28%), because of anatomic reasons (32%), tumor progression (18%), severe toxicity (6%), patient refusal (6%), or noncompliance (38%). These patients completed treatment by external radiation extradose. The median total dose delivered to point A was 70 Gy (range, 10.5 to 105 Gy) (Fig 4). In particular, patients who underwent external RT only and external RT followed by brachytherapy received a median total dose of 61.1 Gy (range, 10.5 to 76.8 Gy) and 71.3 Gy (range, 44 to 105 Gy), respectively. Overall, the median time of radiation treatment delivery was 62 days (range, 11 to 135 days). In particular, 44% of patients required less than 8 weeks, and 27% required more than 100 weeks. For patients who completed treatment with curative intent, the median total dose at point A was 71 Gy (range, 60 to 105 Gy), with a median total duration of therapy of 58 days (range, 33 to 87 days). Two of seven patients initially diagnosed as having metastatic aortic nodes were eligible for and underwent extended-field radiation. Compliance with the planned radiation schedule was relatively acceptable, with 72% of patients receiving treatment according to the protocol. Discontinuation of therapy due to toxicity occurred only in one patient (0.6%) and was due to progressive disease in nine patients (5%). Pelvic control was achieved in 99 patients, ie, 50% of the eligible patients.

*Treatment-Related Morbidity*

Both treatments were well tolerated, and no treatment-related deaths were reported. Table 2 summarizes the severe morbidity of the two treatments. Overall, severe (Chassagne

**Table 2. Severe Morbidity by Treatment Arm**

| Toxicity | NACT (n = 201) | | RS (n = 164) | | RT (n = 177) | |
|---|---|---|---|---|---|---|
| | No. of Events | % | No. of Events | % | No. of Events | % |
| Gastrointestinal | 52 | 26 | 4 | 2 | 10 | 6 |
| Urinary | 3 | 1 | 23 | 14 | 6 | 3 |
| Cardiovascular | 1* | 0.5 | 16 | 10 | — | — |
| Hematopoietic | 49 | 24 | — | — | 1 | 0.6 |
| Cutaneous | 75† | 37 | 8 | 5 | 5 | 3 |
| Peripheral nerve symptoms | 1 | 0.5 | 1 | 0.6 | — | — |
| Vaginal | — | — | 16 | 10 | 29 | 16 |
| Total patients | 55 | 27 | 52 | 32 | 49 | 28 |

NOTE. NACT severe (grade 3 or 4) induced toxicity was evaluated according to WHO criteria; other severe (grade 2 or 3) toxicities were graded according to the French-Italian Glossary of Complications. Some patients had more than one complication.

*Transient cardiac arrhythmia.

†Hair loss.

grade 2 to 3) complications affected 52 (32%) and 49 patients (28%) in the chemosurgery and radiotherapy arms, respectively. Moreover, a 27% severe (World Health Organization grade 3 to 4) additional toxicity was considered for the NACT group (see also Chemotherapy, above). Short-term (within 30 days from the end of treatment) severe complications affected 25 patients (15%) undergoing surgery. In particular, there were no intraoperative severe complications; however, accidental injuries to vessels, requiring additional blood transfusion(s), occurred in nine cases (5%). Bladder dysfunction (17%) and lymphocysts (18%) were the most frequent postoperative complications, but they were severe only in three (2%) and 13 cases (8%), respectively. Less frequent short-term severe complications were abdominal wound dehiscence (2%), ureteral stenosis/fistula (1%), rectovaginal fistula (1%), small bowel infarction (0.6%), and transient leg paresis (0.6%). RT-induced short-term severe toxicity occurred in nine patients (5%). Adverse effects consisted mainly of acute proctitis/cystitis (8%), but they were rarely (2%) severe. Other effects were diarrhea (1%), symptomatic cutaneus edema (1%), myelodepression (0.6%), and uterine perforation (0.6%) requiring treatment discontinuation.

Long-term severe complications occurred in 32 patients (19.5%) from the NACT arm. Dyspareunia affected 10% of patients and represented the most frequent late complication, followed by chronic neurologic bladder (7%), vesico-, ureteral-, or rectovaginal fistulas (3%), laparocele (3%), persistent lymphocysts (2%), and chronic cystitis (1%). Late severe morbidity of RT was observed in 39 patients (22%), consisting mainly of vaginal stenosis/dyspareunia (16%). Less frequent complications were hydronephrosis (2.2%), pelvic fibrosis (1.6%), enterovaginal fistula (1%), chronic cystitis (0.6%), bowel occlusion (1%), malabsorption (0.6%), and fecal incontinence (0.5%).

The relative risk of long-term severe complications for chemosurgery versus RT alone was 0.86 (95% confidence interval [CI], 0.49 to 1.50). Moreover, it is to be considered that 38 (23%) of the patients operated on underwent adjuvant radiotherapy and that 30% of these patients will present with late severe complications.

*Survival*

Survival analysis was done on an intention-to-treat basis on all 441 randomized patients (227 NACT&RS patients, 214 RT patients). Moreover, separate analyses were conducted on the 409 eligible patients (210 NACT&RS patients, 199 RT patients) and on the 295 patients receiving treatment according to the protocol (152 NACT&RS patients, 143 RT patients).

The median possible duration of participation in the study was 79 months (range, 42 to 120 months). The median follow-up of the overall population was 40 months (range, 1 to 107 months). When the analysis was restricted to surviving patients, the median duration of follow-up was 53 months (range, 3 to 107 months). Eight patients (2%) were lost to follow-up, and 21 (5%) died of intercurrent disease.

In the intention-to-treat analysis, the 5-year overall survival rates for patients undergoing NACT&RS and RT were 56.5% (95% CI, 49.2% to 63.7%) and 44.4% (95% CI, 36.4% to 52.4%), respectively ($P = .01$). The approximate 10% survival increase for patients in the NACT arm was confirmed by the analysis of eligible patients: 58.9% (95% CI, 51.4% to 66.3%) *v* 44.5% (95% CI, 36.3% to 52.7%) ($P = .007$). This difference was also observed when the analysis was restricted to patients receiving treatment according to the protocol: 60.2% (95% CI, 51.8% to 68.6%) *v* 46.8% (95% CI, 37.4% to 56.2%) ($P = .02$) (Fig 5). Progression-free survival analyses showed approximately the same differences between the two arms: 55.4% (95% CI, 47.9% to 62.8%) *v* 41.3% (95% CI, 31.7% to 50.9%) ($P = .02$) for the eligible patients, and 56.9% (95% CI, 48.5% to 65.3%) *v* 47.8% (95% CI, 39.2% to 56.4%) ($P = .03$) for those treated according to the protocol (Fig 6).

The 5-year survival analyses by FIGO stage again showed significantly longer overall survival (64.7% [95% CI, 56.5% to 72.9%] *v* 46.4% [95% CI, 37.2% to 55.6%], $P = .005$) and progression-free survival (59.7% [95% CI, 51.3% to 68.1%] *v* 46.7% [95% CI, 38.1% to 55.3%], $P = .02$) for the stage IB2 to IIB patients in the NACT arm compared with the RT arm, respectively (Fig 7). Separate analyses by stage subgroup confirmed the significant differences in overall survival (68.9% [95% CI, 56.9% to 81.3%] *v* 50.7% [95% CI, 38.8% to 63.2%], $P = .01$) and

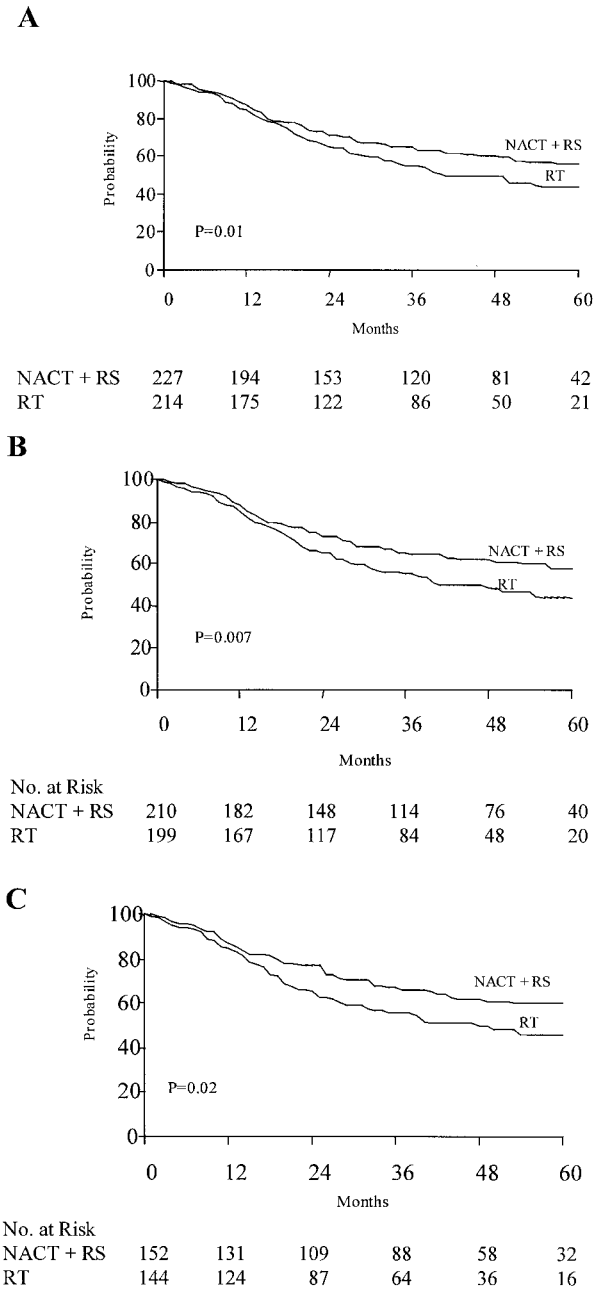


**Fig 5. Overall survival of (A) all randomized patients, (B) eligible patients, and (C) patients treated according to the protocol.**

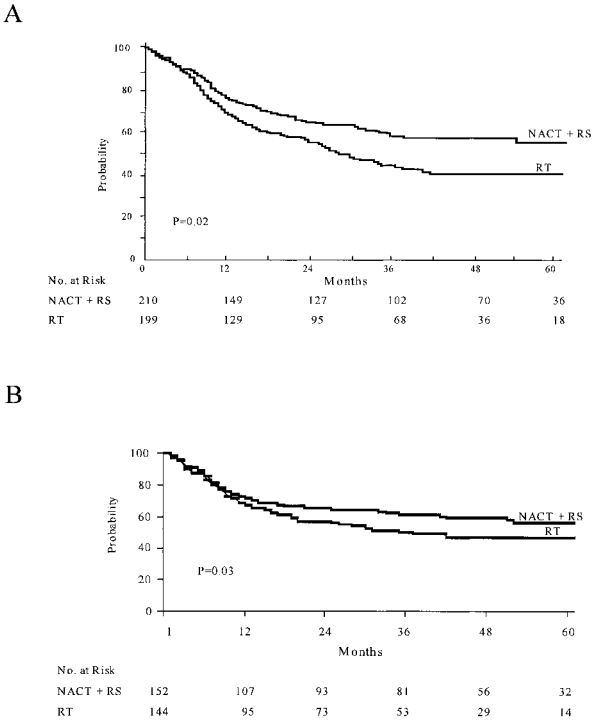


**Fig 6. Progression-free survival of (A) eligible patients and (B) patients treated according to the protocol.**

progression-free survival (65.4% [95% CI, 55.1% to 75.2% *v* 50.6% [95% CI, 40.4% to 60.3%], $P = .01$) for stage IB2 to IIA more than 4 cm but not for stage IIB (overall survival: 58.6% [95% CI, 46.3% to 60.3% *v* 42%, 95% CI, 28.4% to 56.5%, $P = .15$; progression-free survival: 53.2%, 95% CI, 40.8% to 65.4% *v* 42.8%, 95% CI, 29.1% to 57.2%, $P = .51$). Survival rates for the stage III patients did not significantly differ in the two arms (overall survival: 41.6% [95% CI, 26.5% to 56.7%] *v* 36.7% [95% CI, 19.6% to 53.7%], $P = .36$; progression-free survival: 41.9% [95% CI, 27.4% to 56.4%] *v* 36.4% [95% CI, 20.1% to 52.7%], $P = .29$) (Fig 8).

The results of univariate and multivariate analyses are shown in Table 3 and 4. Significant variables in both overall and progression-free survival analyses were FIGO stage, cervical tumor diameter, lymph node status at computed tomography/lymphangiography, and treatment delivered. In particular, the relative risks of overall and progression-free survival for NACT&RS versus RT were 0.63 (95% CI, 0.47 to 0.86) and 0.67 (95% CI, 0.49 to 0.90), respectively.

Overall, 184 patients (45%) developed progressive disease: 84 (40%) in the chemosurgery arm and 100 (50%) in the RT arm. Of these patients, 153 (83%) died of disease, whereas seven (8%) and three (3%) in the NACT and RT arms, respectively, were rescued by salvage treatments. As far as the pattern of progression is concerned, a distant component was present in 59 cases (32%): 31 (37%) and 28 (28%) in the NACT and RT arms, respectively. These differences were not statistically significant. In patients whose treatment was completed according to the protocol,

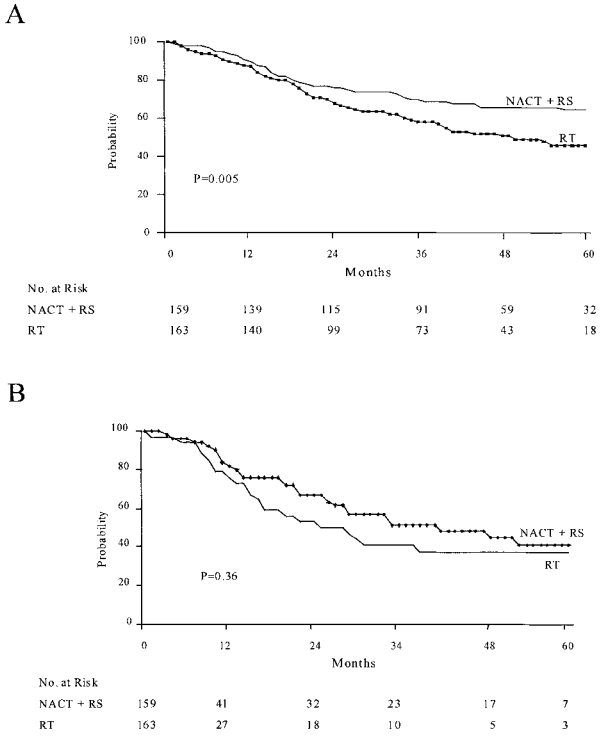


**Fig 7. Stage IB2 to IIB: (A) overall survival; (B) progression-free survival.**

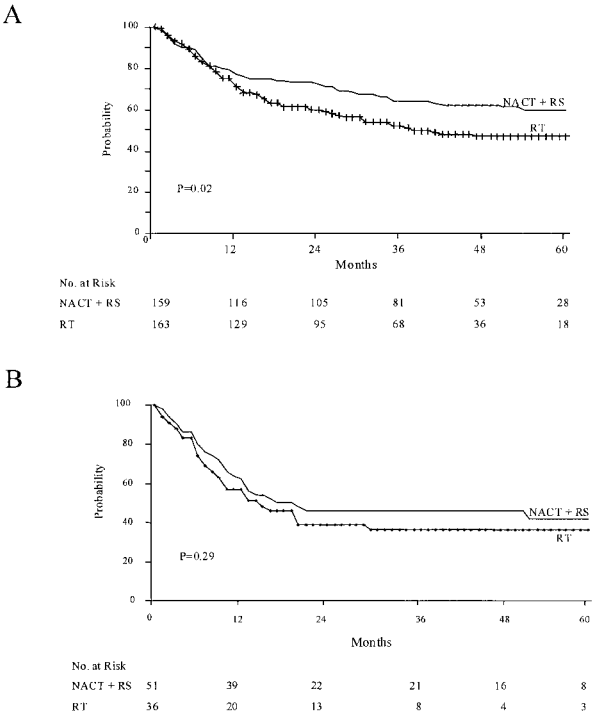


**Fig 8. Stage III: (A) overall survival; (B) progression-free survival.**

81.5% of pelvic progressions and 76% of distant progressions developed within 2 years from the end of primary therapy. Timing by pattern of progression did not significantly differ between the two arms.

## DISCUSSION

In our study, we found that sequential NACT and RS was more effective than exclusive RT in the cure of locally advanced squamous cell cervical cancer. At 5 years, there was a 10% to 15% survival advantage for patients in the experimental arm included in the intention-to-treat analysis ($P = .01$). The statistically significant difference was confirmed by separate analyses conducted on eligible patients ($P = .007$) and on those receiving treatment according to the protocol ($P = .02$). The progression-free survival analyses still confirmed such a therapeutic advantage. Chemotherapy-induced tumor shrinkage rendered radical excision possible in a high percentage of cases, and longer overall and progression-free survival rates were observed in the chemosurgery arm. Although there was increased, but reversible, hematologic toxicity due to chemotherapy, the incidence of long-term complications was similar in the two treatment groups.

The positive impact of sequential NACT&RS on survival was also supported by the results of multivariate analyses of both overall and progression-free survival. In fact, treatment delivered was included among variables significantly affecting the clinical outcome.

**Table 3. Univariate and Multivariate Analyses of Overall Survival**

| | Univariate *P* | Multivariate *P* | Relative Risk | 95% CI |
|---|---|---|---|---|
| Treatment group | | | | |
| NACT + RS | .01 | .004 | 0.63 | 0.47-0.86 |
| RT | | | | |
| FIGO stage | | | | |
| IB2 to IIB | .005 | .02 | 0.61 | 0.43-0.87 |
| III | | | | |
| Age | | | | |
| ≤ 60 years | NS | NS | — | — |
| > 60 years | | | | |
| Cervical tumor size | | | | |
| 4 cm | .0008 | .008 | 0.66 | 0.47-0.90 |
| ≥ 5 cm | | | | |
| Lymph node status* | | | | |
| Negative | .0001 | .001 | 0.53 | 0.38-0.74 |
| Positive | | | | |

*Lymph node status was assessed at the staging work-up by computed tomography/magnetic resonance imaging or lymphangiography.

Abbreviations: CI, confidence interval; NS, not significant.

**Table 4. Univariate and Multivariate Analyses of Progression-Free Survival**

| | Univariate *P* | Multivariate *P* | Relative Risk | 95% CI |
|---|---|---|---|---|
| Treatment group | | | | |
| NACT + RS | .02 | .008 | 0.67 | 0.49-0.90 |
| RT | | | | |
| FIGO stage | | | | |
| IB2 to IIB | .004 | .02 | 0.63 | 0.45-0.89 |
| III | | | | |
| Age | | | | |
| ≤ 60 years | NS | NS | — | — |
| > 60 years | | | | |
| Cervical tumor size | | | | |
| 4 cm | .009 | .05 | 0.74 | 0.54-1.00 |
| ≥ 5 cm | | | | |
| Lymph node status* | | | | |
| Negative | .0001 | .008 | 0.54 | 0.39-0.76 |
| Positive | | | | |

*Lymph node status was assessed at the staging work-up by computed tomography/magnetic resonance imaging or lymphangiography.

The analysis of both overall and progression-free survival by FIGO stage revealed a significant increase for stage IB2 to IIB, whereas only a statistical trend was detected for the more advanced stage group. These data are in accordance with our previous results suggesting that the more advanced the stage, the more limited the benefit achievable by NACT followed by surgery. This could be satisfactorily explained by the direct correlations between disease volume, chemoresponsiveness, radical operability, and outcome in many solid tumors, including cervical cancer.[6,14-17,27] The greater the volume, the larger is the hypoxic and resting phases cell population with reduced or no chemosensitivity and the probability of developing resistant clones. The tumor extent, however it is expressed (ie, FIGO stage, cervical tumor size), is highly predictive of response, which, in turn, significantly affects radical resectability and therapeutic outcome.[14-17] In fact, RS was feasible in 55% of stage III patients compared with 85.5% of those presenting with a less advanced stage ($P < .0001$). Moreover, the evaluation of surgical specimens from radically operated patients revealed a higher incidence of persistent tumor in the parametria and lymph nodes for stage III (50%) compared with stage IB2 to IIB (37%).

About one third of failures showed a distant component. Interestingly, there was no statistically significant difference between the two arms with regard to the pattern of disease recurrence. These data are in accordance with those reported by the Argentine group[28-30] and suggest that the relatively short duration of NACT may be not enough to sterilize distant micrometastases.

Overall, given the multicenter study setting, treatment compliance was acceptable, with approximately 75% of treatments delivered according to the protocol. In the NACT&RS arm, violations mostly concerned surgery (19%) rather than chemotherapy (6%) and were due to inadequate surgical excision of primary tumor and/or lymph nodes. With respect to RT, inadequacy of treatment was generally due to variation in the dose (11%) and/or time of delivery (9%). A median total dose at point A of 70 Gy (range, 10.5 to 105 Gy) delivered in 62 days (range, 11 to 135 days) seems to be lower than that considered optimal RT in advanced cervical cancer. In this setting, 80 to 90 Gy are now considered adequate doses at point A to be delivered over a limited treatment time.[31] Moreover, the inability to apply intracavitary radiation in 28% of these patients because of anatomic reasons was disappointing. However, survival results achieved by exclusive RT in the present study (5-year progression-free survival, 41.3%) seem to be comparable to those recently reported (40%) from a randomized trial with higher average doses delivered to point A (89 Gy; median duration, 58 days).[32] In the present trial, the incidence of clinically detectable aortic metastasis was less than 5%, although it is known that no imaging technique is capable of detecting microscopic aortic metastasis. On the other hand, the role of prophylactic extended-field radiation is still controversial. This is why extended-field radiation was reserved only for patients with evident aortic metastasis who achieved pelvic complete remission.

Nearly all phase II and phase III trials have demonstrated the feasibility of the combination of NACT with both RT or surgery.[6-17,28-30,33-37,39] In the present study, there was no statistical evidence for an excess of severe complications in one of the two arms, although approximately 30% of severe transient—mostly hematologic—toxicity is to be further considered for the NACT group. Severe morbidity is, however, associated with both treatment strategies in approximately 30% of cases. In particular, the addition of RT in about one fourth of radically operated patients may have affected long-term morbidity, with uncertainty about its therapeutic value. Overall, no treatment-related deaths were reported, and the most severe late complications, such as vaginal stenosis/dyspareunia, chronic neurologic bladder, and vaginal fistulas, occurred in less than 20% of patients.

Most of the randomized studies investigating the role of NACT compared the combination of NACT and RT with RT alone, with no evidence of a significant survival benefit by the addition of NACT.[36] The cross-resistance between platinum-based chemotherapy and radiation has been suggested as one of the explanatory mechanisms of such a phenomenon[40] However, the lack of improvement, or even

worsening, in survival in the presence of substantial clinical response leaves room for other hypotheses involving possible changes in tumor cell kinetics induced by upfront chemotherapy.

On the other hand, the removal of residual disease after tumor shrinkage induced by chemotherapy may overcome cell kinetics–based changes resulting in the lack of disease control by RT. Although such a strategy seemed to be associated with improved outcomes on the basis of phase II studies,[5-17] few randomized trials have investigated the use of NACT followed by RS. At the time of this writing, only two randomized trials have been published[28-30,38,39]; another one is still in progress (Gynecologic Oncology Group study 141). To our knowledge, our study is the first European phase III trial for which mature data are reported. Nevertheless, the national dimension of the study must be taken into the account; the results may be limited to Italy. In the Argentine trials, the chemosurgical sequence always resulted in the most efficacious treatment in terms of survival for stage IB2, IIB, and IIIB disease when compared with surgery alone, with chemotherapy followed by radiation or exclusive RT.[28-30,37] However, contrary to the current trial, postoperative external-beam radiation was always included in these trials' designs. In our study, in fact, adjuvant RT was given according to the protocol only to 23% of the entire operated group. In particular, it was given to 21% and to 32% of stage IB2 to IIB and stage III patients, respectively. While the use of adjuvant RT in the less advanced stage subgroup remains of uncertain value, the routine addition of RT performed in the Argentine trials may be advantageous for a better local control in the more advanced stage subset. This might explain the higher survival rate (63%) reported by Sardi et al[30] for the stage IIIB patients treated with NACT&RS followed by RT compared with our results (42%), which were almost superimposable with those achieved by exclusive RT (37%). Strategies involving integrated therapy, particularly with regard to concurrent chemoradiation, have been investigated recently. In this respect, data are now available from large randomized trials in favor of the concurrent use of chemotherapy and RT in a spectrum of advanced disease ranging from stage IB2 through stage IVA.[32,41,42] The addition of chemotherapy significantly increased the rate of pelvic control and, consequently, patient survival, indicating that such an integrated treatment is the likely new gold standard in the treatment of locally advanced disease. Promising results have also been generated within our group with regard to concurrent chemoradiation in a phase II setting.[43] Therefore, based on this evidence and on the data from the present study, a new, prospective, randomized, innovative trial comparing NACT and RS with chemoradiotherapy seems to be worthwhile.

## APPENDIX

The appendix is available online at www.jco.org.

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